

## Article (refereed) - postprint

---

Johnson, Andrew C.; Dumont, Egon; Williams, Richard J.; Oldenkamp, Rik; Cisowska, Iwona; Sumpter, John P. 2013. **Do concentrations of ethinylestradiol, estradiol and diclofenac in European rivers exceed proposed EU environmental quality standards?** *Environmental Science and Technology*, 47 (21). 12297-12304. [10.1021/es4030035](https://doi.org/10.1021/es4030035)

© 2013 American Chemical Society

This version available <http://nora.nerc.ac.uk/503779/>

NERC has developed NORA to enable users to access research outputs wholly or partially funded by NERC. Copyright and other rights for material on this site are retained by the rights owners. Users should read the terms and conditions of use of this material at

<http://nora.nerc.ac.uk/policies.html#access>

**This document is the author's final manuscript version of the journal article, incorporating any revisions agreed during the peer review process. Some differences between this and the publisher's version remain. You are advised to consult the publisher's version if you wish to cite from this article.**

The definitive version is available at [www.acs.org](http://www.acs.org)

Contact CEH NORA team at  
[noraceh@ceh.ac.uk](mailto:noraceh@ceh.ac.uk)

1 **Do concentrations of ethinylestradiol, estradiol and diclofenac in European rivers exceed**  
2 **proposed EU environmental quality standards?**

3 ANDREW C. JOHNSON\*† EGON DUMONT†, RICHARD J. WILLIAMS†, RIK OLDENKAMP‡, IWONA  
4 CISOWSKA† and JOHN P. SUMPTER§

5 †Centre for Ecology and Hydrology, Wallingford, Oxfordshire, OX10 8BB, UK

6 ‡Department of Environmental Science, Radboud University, Nijmegen, NL-6500 GL , The Netherlands

7 §Institute for the Environment, Brunel University, Uxbridge, UB8 3PH, UK

8

---

9 This study used a geographic based water model to predict the environmental concentrations of  
10 three pharmaceuticals 17 $\alpha$ -ethinylestradiol (EE2), 17 $\beta$ -estradiol (E2) and diclofenac throughout  
11 European rivers. The work was prompted by the proposal of the European Community  
12 (COM(2011)876) to consider these chemicals as candidates for future control via environmental  
13 quality standards (EQS). National drug consumption information, excretion, national water use, and  
14 sewage removal rates, were used to derive per capita sewage effluent values for the European  
15 countries . For E2, excretion rates of the natural hormone and national demographics were also  
16 included. Incorporating this information into the GWAVA model allowed water concentrations  
17 throughout Europe's rivers to be predicted. The mean concentration from the expected sewage  
18 discharge scenario indicated that 12% by length of Europe's rivers would reach concentrations  
19 greater than the proposed 0.035 ng/L EQS for EE2. For several countries, between a quarter and a  
20 third of their total river length would fail such an EE2 EQS. For E2, just over 1% by length of rivers  
21 would reach concentrations greater than the 0.4 ng/L proposed EQS, whilst just over 2% by length of  
22 rivers would reach concentrations greater than the proposed EQS of 100 ng/L for diclofenac.

23 **Key words**

24 Ethinylestradiol, estradiol, diclofenac, river water, model, prediction, environmental quality  
25 standard, Europe

26 **Introduction**

27 The control of what are called hazardous substances in Europe falls under the Water Framework  
28 Directive (WFD). When an environmental quality standard (EQS) is set for a chemical this can lead to  
29 it being phased out of production. However, the very recent addition of the pharmaceuticals 17a-  
30 ethinylestradiol (EE2), 17b-estradiol (E2) and diclofenac in the European Community document  
31 (COM(2011)876) appear to usher in a new era. This document suggested annual average EQS of  
32 0.035 ng/L for EE2, 0.4 ng/L for E2 and 100 ng/L for diclofenac. Now this document has been  
33 amended and these drugs put on a watch list until they are reviewed again in 2014. Thus, there  
34 remains the possibility that they will become controlled with an EQS in due course.

35           Given their societal health benefits, it is unlikely and perhaps undesirable for particular  
36 pharmaceuticals to be phased out on the basis of environmental concerns. Thus, as source controls  
37 are inappropriate, so end of pipe solutions may have to be sought. A number of studies have  
38 examined the efficacy of different sewage tertiary treatments and indeed one European State,  
39 Switzerland, is planning to invest in such technology [1]. Based on our current knowledge, most of  
40 the proposed techniques would appear to be very expensive to build and maintain [2, 3]. As an EQS  
41 would be set for the receiving waters and not the sewage effluent, so the extent of investment will  
42 depend on the available dilution. Thus, the magnitude of the challenge for different nations will  
43 reflect their unique geographical and hydrological circumstances. Examining the extent of these  
44 differences in national exposure would appear to be vital information in engaging not only  
45 regulators, water utilities, government and environmental scientists, but also the general public too.

46           Geographic-based water quality models are a practical tool that can address the question of  
47 exposure to pharmaceuticals at a continental scale. Measuring all of these chemicals throughout  
48 every European river would be exceedingly costly and time consuming, to say nothing of the  
49 problems of consistency. Measuring EE2 throughout Europe's rivers would be impractical, since very  
50 few, if any, chemists can confidently claim to quantify EE2 at concentrations of 0.035 ng/L with

51 current technology. The strengths and weaknesses of water quality modelling vs measuring have  
52 been reviewed before, but it is important to note that models have no lower detection limit [4]!

53 Before considering how to approach this task, it is worth briefly reviewing what evidence  
54 brought these chemicals to the attention of the EU. Following a series of surprising observations on  
55 the effects of fish being exposed to sewage effluent in the mid 1980s' in the UK, a series of  
56 methodical studies were carried out which revealed that something in effluent could provoke  
57 endocrine disruption [5]. Field surveys then revealed that endocrine disruption of fish was  
58 widespread in wild fish caught in proximity to sewage treatment plants [6] and that the most potent  
59 component of that effluent was the fraction containing steroid estrogens [7]. Amongst those steroid  
60 estrogens, E2 and the synthetic estrogen EE2 were demonstrated to be the most potent [8]. These  
61 observations were repeated by scientists throughout the world. Whilst the disrupting effects of E2  
62 and EE2 at low ng/L exposure concentrations on individual fish are undeniable, the assessment of  
63 the effect of that disruption on fish populations is less secure [9]. Diclofenac came to prominence  
64 when it was strongly implicated in the poisoning and decline of vulture populations in Asia [10]. A  
65 number of studies have suggested that low µg/L concentrations of diclofenac adversely affect fish  
66 [11, 12], and raised concern that diclofenac might pose a threat to wild fish. However, a recent  
67 study failed to support the results of these earlier studies, and instead found that adverse effects on  
68 fish occurred only when the environmental concentration approached 1mg/L [13], which is very  
69 much higher than any river concentration is likely to be.

70 If these pharmaceuticals stay on the watch list and even become priority substances needing  
71 control, so it is likely other pharmaceuticals will follow. A stated objective of the European  
72 Parliament legislative resolution of 2 July 2013 amending Directives 2000/60/EC and 2008/105/EC as  
73 regarding putting chemicals on a watch list (COM(2011)0876 – C7-0026/2012 – 2011/0429(COD)) is  
74 that this will stimulate further studies both in terms of monitoring and on the risks they pose. To  
75 respond the objectives of this study were:

- 76       • To refine and adapt existing models for E2, EE2 and diclofenac using the most recent  
77           consumption information to predict European river water concentrations
- 78       • To examine how close predicted river concentrations would exceed proposed EQS levels of  
79           0.4 ng/L for E2, 0.035 ng/L EE2 and 100 ng/L diclofenac across Europe
- 80       • To identify the European countries most likely to be challenged if such EQS levels had to be  
81           achieved.

## 82   **Materials and methods**

83   **Assessing per capita consumption rates.** The approach to estimating sewage effluent  
84   concentrations takes the drug consumption per capita for a specific nation, less that prevented from  
85   being excreted as the free parent compound, and less that removed in sewage treatment. The  
86   effluent concentration is then calculated by dividing this figure by the per capita wastewater  
87   discharge for that nation:

88

$$89 \qquad W = \frac{(C - E - S)}{D}$$

90

91   Where  $C$  is consumption of the drug as ng/cap/d;  $E$  is the amount of the drug that is not excreted  
92   (ng/cap/d);  $S$  is the amount of the drug that is prevented from escaping into sewage effluent  
93   (ng/cap/d);  $D$  is the diluting volume of wastewater as L/cap/d; and  $W$  is the effluent concentration as  
94   ng/L.

95   The river concentration at the point of the effluent discharge ( $R_m$ , ng/L) is calculated by mass  
96   balance, and loss of the compound due to aquatic processes such as sedimentation and  
97   transformation is accounted for with a first order dissipation process to give the downstream  
98   concentration ( $R_d$ , ng/L).

99

$$R_d = R_m e^{-k t}$$

100 Where,  $k$  is the decay rate ( $\text{days}^{-1}$ ) and  $t$  is the time of travel (days). The time of travel is the river  
101 reach volume divided by the flow rate [14].

102 The most critical part of any predictive model used to assess concentrations of human  
103 derived chemicals in water is obtaining information on usage. National databases and academic  
104 studies can be interrogated to assess a per capita consumption value, given the human population of  
105 the country at that time (Table 1).

106 **TABLE 1. Range of national pharmaceutical per capita consumption values and their year of origin**

Country	EE2 consumption ( $\mu\text{g}/\text{cap}/\text{d}$ )	Ref source	E2 (HRT) consumption ( $\mu\text{g}/\text{cap}/\text{d}$ )*	Ref Source	Diclofenac consumption ( $\mu\text{g}/\text{cap}/\text{d}$ )	Ref Source
Belgium	2.11 (2007)	[15]	NA	NA	NA	NA
France	1.54 (2007)	[15]	NA	NA	449 (2004)	[16]
Germany	1.69 (2007)	[15]	NA	NA	2613 (2003)	[17]
Italy	0.94 (2007)	[15]	NA	NA	NA	NA
Netherlands	2.59 (2012)	[18]	1.7 (2011)	GIPdatabank (www.gipdatabank.nl)	1205 (2012)	[18]
UK	1.21 (2007)	[15]	5.7 (2010)	NHS dataset (www.ic.nhs.uk)	957 (2010)	NHS dataset (www.ic.nhs.uk)
Spain	1.0 (2003)	[19]	NA	NA	2124 (2003)	[19]
Sweden	0.84 (2010)	Apotekensservice (www.apotekensservice.se)	15.7 (2010)	Apotekensservice (www.apotekensservice.se)	1351 (2010)	Apotekensservice (www.apotekensservice.se)
Poland	1.0 (2000)	[20]	NA	NA	1482 (2000)	[20]
Switzerland	2.0 (2000)	[19]	NA	NA	1459 (2000)	[19]
Denmark	NA†	NA	NA	NA	520 (2009)	Danish medicine statistics (www.ssi.dk)
Czech Republic	1.18 (2012)	SUKL database (www.sukl.cz)	4.1 (2012)	SUKL database (www.sukl.cz)	1075 (2012)	SUKL database (www.sukl.cz)
Norway	1.51 (2011)	Norwegian Prescription Database (www.norpd.no)	7.9 (2011)	Norwegian Prescription Database (www.norpd.no)	1059 (2011)	Norwegian Prescription Database (www.norpd.no)
Mean	<b>1.47</b>		<b>7.0</b>		<b>1299</b>	

107 †NA = Not Available \*HRT = Hormone Replacement Therapy

108 **Ethinylestradiol consumption, excretion, and environmental fate.** Recent values for EE2  
109 consumption in different European countries that are available show only a small variation in  
110 individual EE2 consumption values (Table 1 & 2). The probable excretion rate of EE2 by humans has

111 been extensively reviewed [21] and this also shows only modest variation (Table 2). Information on  
112 removal in sewage treatment is available [21-27] and a wide variation in performance is apparent  
113 (Table 2). EE2 is still considered the most persistent of the steroid estrogens ,with a modest half  
114 life in water of 17 d and also a slow photodegradation rate [28, 29]. The model used here for  
115 predicting EE2 concentrations in sewage effluent and receiving waters [21] has been compared  
116 previously against measured concentrations [30-32]. An agreement value can be given by dividing  
117 the observed by the modelled concentration, such that one is a perfect match, less than one an  
118 overestimate and greater than one an underestimate. For EE2 the result is 0.2-2.0 (n=20) for these  
119 studies which is within an order of magnitude difference [30, 31].

120 **Estradiol consumption, excretion, and environmental fate.** Estradiol is one of the natural estrogen  
121 hormones circulating in the human body and is indeed common to all vertebrates [33]. It is also  
122 provided as an active ingredient of many hormone replacement therapies (HRT) and as an ester pro  
123 drug (estradiol valerate) in some new contraceptive formulations. The most important contributors  
124 of natural E2 are pregnant women, providing an estimated 63% of the natural E2 load in the UK [21],  
125 followed by menstrual women (18%). For this study the demographics of each European nation was  
126 assessed and the number of males, menstrual, menopausal and pregnant females recorded [34]. To  
127 calculate a per capita E2 discharge for each nation, the assumed E2 excretion rate ( $\mu\text{g}/\text{cap}/\text{d}$ ) for  
128 each population sub-group [21] was multiplied by the number of people in each category. It should  
129 be noted that obtaining a value for the number of pregnant women is particularly complex as  
130 abortions, foetal deaths, live births and multiple births for each country have to be disentangled  
131 from a range of sources. This value was normalised by dividing by the total population to give a per  
132 capita natural E2 value. To this natural E2 value was added the per capita HRT E2 value  
133 where known, or otherwise a European average value, to calculate a national total E2 discharge  
134 value (Table 2). Recently, the topic of human E2 excretion was reviewed [35] for the US and a value  
135 of  $7.87 \mu\text{g}/\text{cap}/\text{d}$  was reported, which is very similar to that previously calculated for E2 [21] in the  
136 UK and the range calculated for this study ( $4-8 \mu\text{g}/\text{cap}/\text{d}$ ).

137            Given the amount of E2 excreted by women on HRT and the proportion present as the  
138 parent or glucuronide then only 3-10% of the pharmaceutical E2 ingested would be excreted [21, 36,  
139 37]. This implies that for the countries for which we have data (Table 1), only 1-8% of the total E2  
140 arriving at a sewage treatment plant (STP) would have originated from pharmaceutical sources.

141            It was assumed that 50% of E2 will convert to E1 in the sewers before arriving at a STP  
142 following the suggestion of earlier models [21] (Table 2). Information on removal in sewage  
143 treatment is fairly consistent [22-25, 27, 38-40], with a mean removal of 89% being recorded (Table  
144 2). No type of biological sewage treatment (such as between trickling filter and activated sludge) is  
145 significantly worse than any other in removing E2 [41]. The ready degradability of E2 in river water  
146 samples indicates half-lives of 0.2 to 8.7 d could be expected [28], and the dissipation observed in  
147 the field appears to correspond to such rates [42]. This approach to predicting E2 concentrations in  
148 sewage effluent and receiving waters has been compared previously against measured  
149 concentrations and found to give an observed over modelled agreement ratio of 1.3 (n=3) at one  
150 plant effluent [30] and 0.4 (n=19) for 19 STP effluents with an agreement ratio of 0.5-0.7 for a 34 km  
151 river stretch [31].

152            There is a danger that modelling river E2 concentrations on the basis of human inputs alone  
153 may underestimate the situation in areas where livestock predominate. Whilst some evidence for a  
154 link between the presence of livestock and river estrogens have been made [43] widespread  
155 endocrine disruption remains most closely associated with STPs [32] and E2 river predictions at least  
156 in the UK can be explained by sewage inputs [31, 44].

157 **Diclofenac consumption, excretion, and environmental fate.** Diclofenac (2-[2,6-  
158 dichlorophenyl)amino]benzeneacetic acid is a popular non-steroidal anti-inflammatory drug often  
159 used to treat rheumatic type pain. The variation in national diclofenac consumption rates appears  
160 to be wider than for the other two drugs (Table 1 and 2). The range in diclofenac excretion values  
161 has been reviewed previously [45] and appears to be more variable than the range for EE2. Whilst



162 there again appears to be quite large variability [18, 46-56], the weighted mean sewage removal of  
 163 diclofenac is poor at only 22% (Table 2). Photodegradation has been put forward as an important  
 164 removal mechanism in surface waters [57-59]. In reality, leaving darkness aside, conditions in the  
 165 field are often not ideal for photodegradation, so removal along a river, where residence times are  
 166 typically much shorter than lakes, can be negligible for diclofenac [57, 60]. Given this uncertainty it  
 167 was considered prudent to exclude attenuation in predictions for this molecule in river water. The  
 168 modelling approach for predicting diclofenac concentrations was similar to that carried out  
 169 previously [45], but now with slightly changed parameters (consumption, excretion and sewage  
 170 removal) informed by more recent literature. As this diclofenac method has not been tested  
 171 previously, this was examined using relatively recent sewage effluent measured values from  
 172 composite samples where inhabitant and flow information permitted predictions to be made [18,  
 173 54, 61, 62](Table S1).

174 **TABLE 2. Range of factors affecting the model and their potential impact on the outcome. Note**  
 175 **where sufficient data permits a weighted mean is given followed by the best and worst case value**  
 176 **given in parenthesis.**

Factor	EE2	E2	Diclofenac
Consumption range across nations ( $\mu\text{g}/\text{cap}/\text{d}$ )	0.84-2.59	4.1-8.2 <sup>a</sup>	449-2613
Apparent consumption variation	3-fold	2-fold	6-fold
Weighted mean with lowest and highest patient excretion values (%)	40 (21-54)	NA	9.5 (2-23)
Potential effect on influent concentration	3-fold	NA	11-fold
Weighted mean with lowest and highest sewage treatment removal (%)	68 (0-90)	89 (69-99)	22 (0-82)
Potential effect on sewage effluent concentration	10-fold	31-fold	5-fold
Potential effect on drug concentrations by combining effects of excretion and sewage treatment removal factors.	26-fold	31-fold	64-fold
In stream half-life in days (20°C)	17.3	2.3 (0.3-8.7)	Not used
Range of dilution factors across Europe ( $\text{m}^3/\text{cap}/\text{d}$ ) **		2.8 - 2.7·10 <sup>3</sup>	
Potential effect on water concentration		1000-fold	

177 <sup>a</sup> As E2 is largely an endogenous hormone we cannot discuss it in terms of consumption and excretion rate.  
178 The values given are the concentration excreted by a 'normalised human' [21] modified by national  
179 demographics and HRT use differences where known

180 \*\*10%ile to the 90%ile of dilution values calculated on a cell-by-cell basis using 1970-2000 average river  
181 discharge  
182

183 **European river water modelling.** To examine potential concentrations of these chemicals  
184 throughout European surface waters, the geographic-based water resources model GWAVA run in a  
185 water quality mode was used [14]. This model uses geographic data on the location and size of the  
186 human European population and their association with STPs. The version of GWAVA used here  
187 incorporates a newly available and extensive dataset (2009-2010 information) of locations and  
188 number of people connected to sewage discharge points in Europe [63]. The flows through these  
189 STPs are incorporated with the natural river discharge adjusted for abstractions (principally for  
190 potable supply and agriculture). The hydrology is driven by monthly climate over the period 1970-  
191 2000. The ability of GWAVA to simulate river flows has been previously tested against gauged  
192 flows across Europe, and other continents. Also modelled water quality determinands have been  
193 compared with measured data [14]. The chemical inputs of per capita drug consumption, excretion,  
194 removal in sewage, and in-stream half- life were provided by this study (Table 2). The model  
195 calculates the water concentrations of chemicals through water courses in a series of 177,470 grid  
196 squares (cells) of approximately 6 x 9 km (5 by 5 Arc minutes) dimensions. On a monthly basis, in the  
197 water courses in each cell receiving effluent, the concentration is calculated by diluting the mass of  
198 chemical discharged in the volume of water in the cell accounting for any loads from upstream cells.  
199 The chemicals are transported downstream with the discharge to the next cell. Chemical can be lost  
200 through abstraction or a first-order dissipation process. The time of travel though the gridded  
201 network (which can comprise rivers, lakes and wetlands) is calculated from the river flow rate and  
202 the water volume of each cell. Surface water volumes are estimated using established empirical  
203 relationships with width and depth data [14]. Thus, the model was set up using either the national,  
204 or mean, per capita consumption for EE2 and diclofenac for each country as appropriate (Table 1).

205 For E2, a value for each nation was derived from its population demographics plus pharmaceutical  
206 E2 use where known (Table 1). The mean value for each grid square was then used as the output.  
207 This was considered the most relevant output given that the proposed EQS in the EU  
208 (COM(2011)876) document would use an annual average (AA) value. The model output and its  
209 statistical analysis can be for a continent, for separate nations or even for individual river basins  
210 based on selecting the appropriate cells. Trans-boundary flows and their pollutant load are always  
211 accounted for.

212 **Scenario analysis.** There are uncertainties in the model parameters determining effluent  
213 concentrations, which are critical in estimating river concentrations. In order to assess the impact of  
214 this uncertainty, a series of scenarios were run to establish the range of likely river concentrations  
215 (and hence likely EQS exceedence) , based on the reported literature values. These scenarios were a  
216 best case - low excretion, high sewage removal and high in stream dissipation; a worst case - high  
217 excretion, low removal and slow in stream dissipation and an expected case, which used weighted  
218 average values for these parameters (Table S2). The envelope of possible effluent concentrations  
219 from the best and worse case scenarios was large differing by factors of approximately 26 for EE2, 31  
220 for E1 and 64 for diclofenac (Table 2). The expected scenario based on the mean literature values  
221 gives reasonable agreement with the few available measured data (see above and results section),  
222 with the other cases giving the extreme values.

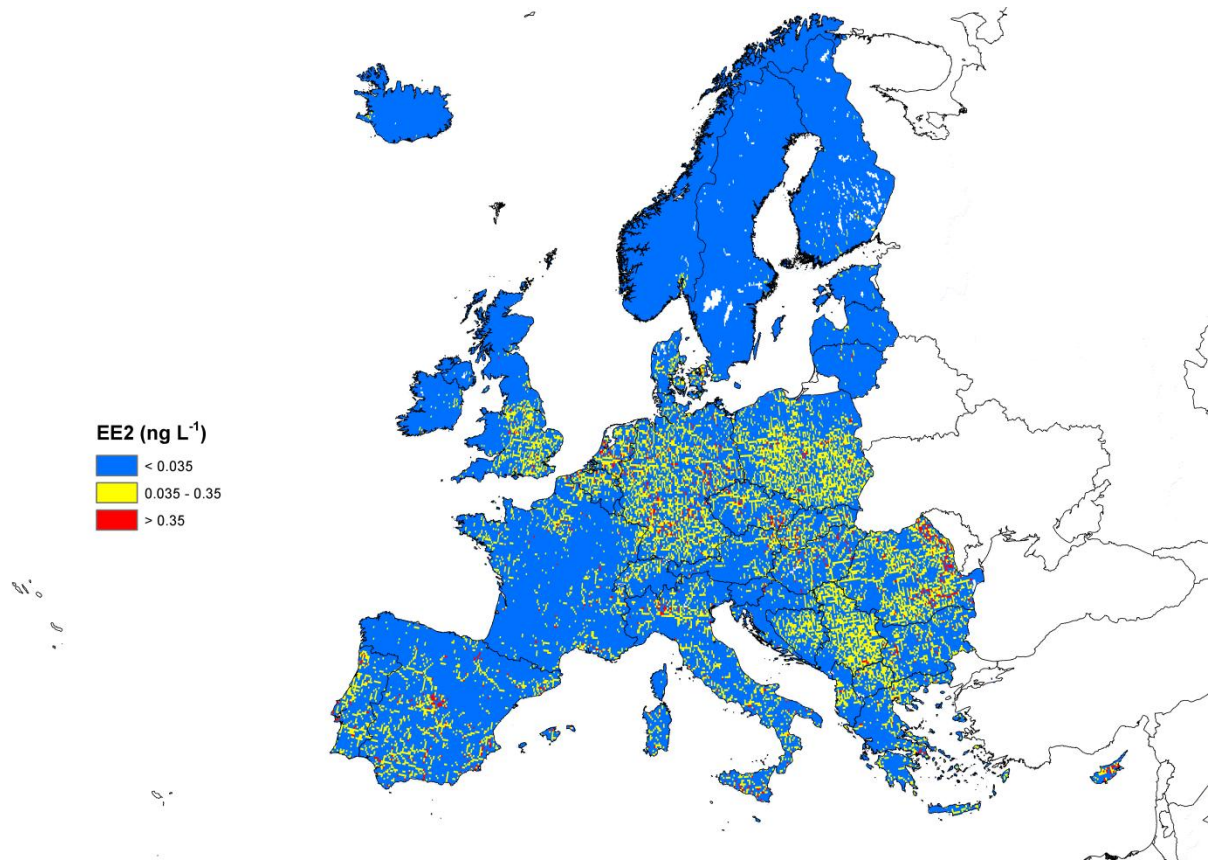
223

## 224 **Results and Discussion**

225 **Ability to predict diclofenac concentrations in effluent.** The predicted and measured effluent  
226 diclofenac concentrations were compared by dividing the measured by the predicted value to give  
227 an agreement ratio (Table S1). Based on this small comparison, with agreement ratios between 0.5

228 and 8.7, it appears the diclofenac predictions were broadly acceptable (Table S1) but with a  
229 tendency to underestimate.

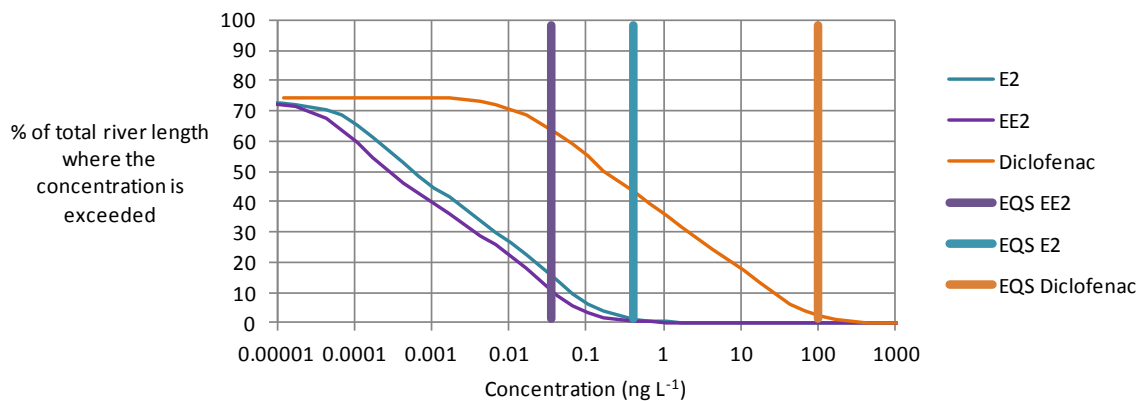
230 **Predicted exceedences of proposed European EQS values.** Before starting the  
231 water quality modelling, based on the European mean consumption values, excretion values and  
232 sewage removal factors (Tables 1 and 2) then 1 ng/L EE2, 3 ng/L E2 and 570 ng/L diclofenac would  
233 be expected in European sewage effluents. It should be noted that where data were lacking, such as  
234 in some Eastern European countries, European average drug consumption values were used. Apart  
235 from predicting the consumption value correctly, it can be seen that variations in the hydrological  
236 dilution component will have the biggest impact on the outcome (Table 2). Rivers where an annual  
237 average concentration of EE2 would exceed 0.035 ng/L would be fairly widespread with the  
238 expected scenario (Fig. 1). Of perhaps greater biological significance is where EE2 concentrations  
239 might exceed 0.35 ng/L [8, 64] and this is far less widespread but not negligible (Fig. 1). When all the  
240 results are plotted as cumulative frequency distributions, both as the expected (Fig. 2) together with  
241 the best and worst case (Fig. S1 and S2) scenarios and compared with the proposed EQS values it can  
242 be seen that EE2 would pose the greatest challenge. It can be observed that 74% of Europe's rivers  
243 by length receive some sewage input whilst the remaining lengths have negligible human input (Fig.  
244 2). Between 2 and 25% by length of Europe's rivers were predicted to have EE2 concentrations in  
245 excess of 0.035 ng/L (best and worst case) with the expected outcome being 12% (Fig. 2). For E2  
246 between 0-6% of river lengths were predicted to exceed 0.4 ng/L (1.5% expected exceedance) and  
247 for diclofenac this is predicted to range from 0.1-8.3% of river lengths exceeding 100 ng/L (2.4%  
248 expected exceedance) in the three scenarios (Fig. 2, Fig. S1 and S2).



249

250 **FIGURE 1. Location of European surface waters where EE2 concentrations are predicted to exceed**  
 251 **0.035 ng/L (yellow) and 0.35 ng/L (red) based on expected chemical discharge (mean excretion**  
 252 **and mean sewage removal)**

253



254

255 **FIGURE 2. Predicted average river water concentrations throughout the European river network**  
 256 **based on expected chemical discharge (mean excretion and mean sewage removal) and their**  
 257 **proximity to the proposed EQS values in COM(2011)876**

258

260 **TABLE 3. Predicted proportion of national river length that would exceed the suggested annual**  
 261 **average EQS based on expected chemical discharge**

EE2 (0.035 ng/L AA EQS)		E2 (0.4 ng/L AA EQS)		Diclofenac (100 ng/L AA EQS)	
>30%	Netherlands, Germany, Macedonia, Romania, Poland, Slovakia, Belgium, Bosnia, Serbia	>5%	Romania*, Czech R., Netherlands	>10%	Germany
25-30%	Czech R., Hungary, England	4-5%	Slovakia, Hungary, Germany, Italy, England	8-10%	Spain, Romania, Netherlands
20-25%	Portugal, Albania, Denmark, Bulgaria, Greece	3-4%	Spain, Portugal, Poland, Denmark, Albania, Belgium, Macedonia	5-8%	Poland, Czech R., Hungary, Italy
15-20%	Italy, Switzerland, Austria,	2-3%	Bulgaria, Luxembourg, Serbia,	3-5%	Slovakia, Portugal, Belgium, Serbia, Macedonia, England
10-15%	Spain, Luxembourg, Croatia	1-2%	Greece, Austria, France,	1-3%	Albania, Bulgaria, Luxembourg, Austria, Greece, Denmark, Switzerland
<10%	France, Ireland, Slovenia, Lithuania, Estonia, Wales/Scotland, Finland, Latvia, Sweden, Norway	<1%	Croatia, Switzerland, Ireland, Slovenia, Lithuania, Estonia, Wales/Scotland, Finland, Latvia, Sweden, Norway, Bosnia	<1%	Croatia, Ireland, Slovenia, France, Lithuania, Estonia, Wales/Scotland, Finland, Latvia, Sweden, Norway, Bosnia

262 \*Values provided for 32 European nations. The UK was separated into England and  
 263 Wales/Scotland/Northern Ireland. Cyprus and Iceland were not included due to uncertainties in the  
 264 ability to simulate their chemical concentrations.  
 265

266 It is possible to examine the proportion of river length that would exceed the suggested EQS on a  
267 national basis in the expected scenario (Table 3). Some countries, such as the Netherlands, Czech  
268 Republic, Romania and Germany appear to have the most exposed rivers, whilst the rivers in the  
269 Scandinavian countries and Baltic Republics are typically least exposed. The high, or low, exposure  
270 of some countries does not always seem intuitive and it is worth reviewing the principal controlling  
271 factors captured in the model predictions:

- 272 • High populations discharging into small rivers.
- 273 • Above, or below average national consumption of the specific drug.
- 274 • Low sewer connection (eg in Belgium only considered to be 60%) as septic tanks are  
275 assumed to not be directly connected to rivers.
- 276 • Receiving waste from upstream neighbouring countries, such as the Netherlands (important  
277 where in-stream attenuation is low).
- 278 • It is the nature of averages that they can be highly influenced by transient very low flows,  
279 which can occur more frequently in some countries than others (eg Spain, Romania and UK).
- 280 • Where the GWAVA model does not have specific information on the sewage effluent  
281 discharge points (eg Poland, Bosnia Herzegovina, Serbia), it estimates a discharge point  
282 relative to the population centre and the nearest water course. This could lead to too high  
283 modelled concentrations as discharge may be incorrectly ascribed to small tributaries.
- 284 • The range of predicted concentrations can be rather narrow in some country's rivers. The  
285 choice of the EQS value can then dramatically change the percentage of river length  
286 exceeding that EQS.

287 The national exposure to these chemicals can only be considered a preliminary guide, but  
288 nevertheless it will hopefully stimulate further study and debate.

289 **Implications.** Given the enormous difficulties in measuring picogram concentrations of E2  
290 and EE2 in rivers, currently our best hope in assessing exposures throughout Europe is through

291 modelling. With its global scope, models like GWAVA can be applied to continents, such as Europe,  
292 to assess possible river concentrations of pollutants originating from the human population.  
293 However, with a 6 x 9 km grid cell, its precision is limited and in some countries the sewage effluent  
294 discharge locations are also only estimated. Similarly, in this modelling exercise where the precise  
295 national consumption of a drug was not known, a European mean had to be applied. Despite these  
296 limitations, the clear message from this modelling exercise was that using the expected scenario  
297 over 10% of continental Europe's rivers (25% assuming a worst case scenario) would exceed a 0.035  
298 ng/L EE2 AA EQS. For many European countries, a quarter to a third of their rivers would fail such a  
299 standard. If a 0.035 ng/L EE2 AA EQS were to be applied across Europe, it would represent an  
300 enormous technical and financial challenge to meet, given the extent of likely failure predicted here.

### 301 **Acknowledgements**

302 This study was funded by NERC through its core funding of CEH. The authors are grateful to V. Keller  
303 for help with the modelling. The views expressed are those of the authors alone.

### 304 **Supporting Information Available**

305 Details on the corroboration of predicted and measured diclofenac concentrations in sewage  
306 effluent, cumulative frequency curves for best and worst case scenarios for the pharmaceuticals in  
307 European rivers together with parameters used in the modelling are available free of charge via the  
308 Internet at <http://pubs.acs.org>.

### 309 **Corresponding author**

310 \*Phone +44-1491-692367; fax: +44-1941-692424; e-mail: ajo@ceh.ac.uk

311

### 312 **References**

313 1. FOEN *Micropollutants in municipal wastewater*; Bern, Switzerland, 2012, 2012; p 7.



- 314 2. Koh, Y. K. K.; Chiu, T. Y.; Boobis, A.; Cartmell, E.; Scrimshaw, M. D.; Lester, J. N., Treatment  
315 and removal strategies for estrogens from wastewater. *Environmental Technology* **2008**, *29*,  
316 (3), 245-267.
- 317 3. Butwell, A.; Johnson, I.; W., Y.; Dempsey, P. *Assessment of the potential costs to the water*  
318 *industry of reducing oestrogenic steroid discharges in treated sewage effluent -final report*;  
319 WRc plc, Swindon, Wiltshire, UK: March 2004, 2004; p 80.
- 320 4. Johnson, A. C.; Ternes, T.; Williams, R. J.; Sumpter, J. P., Assessing the concentrations of  
321 polar organic microcontaminants from point sources in the aquatic environment: Measure  
322 or model? *Environmental Science & Technology* **2008**, *42*, (15), 5390-5399.
- 323 5. Purdom, C. E.; Hardiman, P. A.; Bye, V. J.; Eno, N. C.; Tyler, C. R.; Sumpter, J. P., Estrogenic  
324 effects of effluents from sewage treatment works. *Chemical Ecology* **1994**, *8*, 275-285.
- 325 6. Jobling, S.; Nolan, M.; Tyler, C. R.; Brighty, G.; Sumpter, J. P., Widespread sexual disruption in  
326 wild fish. *Environmental Science & Technology* **1998**, *32*, (17), 2498-2506.
- 327 7. Desbrow, C.; Routledge, E. J.; Brighty, G. C.; Sumpter, J. P.; Waldock, M., Identification of  
328 estrogenic chemicals in STW effluent. 1. Chemical fractionation and in vitro biological  
329 screening. *Environmental Science & Technology* **1998**, *32*, (11), 1549-1558.
- 330 8. Caldwell, D. J.; Mastrocco, F.; Anderson, P. D.; Lange, R.; Sumpter, J. P., Predicted-no-effect  
331 concentrations for the steroid estrogens estrone, 17 beta-estradiol, estriol, and 17 alpha-  
332 ethinylestradiol. *Environmental Toxicology and Chemistry* **2012**, *31*, (6), 1396-1406.
- 333 9. Harris, C. A.; Hamilton, P. B.; Runnalls, T. J.; Vinciotti, V.; Henshaw, A.; Hodgson, D.; Coe, T.  
334 S.; Jobling, S.; Tyler, C. R.; Sumpter, J. P., The Consequences of Feminization in Breeding  
335 Groups of Wild Fish. *Environmental Health Perspectives* **2011**, *119*, (3), 306-311.
- 336 10. Oaks, J. L.; Gilbert, M.; Virani, M. Z.; Watson, R. T.; Meteyer, C. U.; Rideout, B. A.;  
337 Shivaprasad, H. L.; Ahmed, S.; Chaudhry, M. J. I.; Arshad, M.; Mahmood, S.; Ali, A.; Khan, A.  
338 A., Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature* **2004**,  
339 *427*, (6975), 630-633.
- 340 11. Hoeger, B.; Kollner, B.; Dietrich, D. R.; Hitzfeld, B., Water-borne diclofenac affects kidney and  
341 gill integrity and selected immune parameters in brown trout (*Salmo trutta f. fario*). *Aquatic*  
342 *Toxicology* **2005**, *75*, (1), 53-64.
- 343 12. Schwaiger, J.; Ferling, H.; Mallow, U.; Wintermayr, H.; Negele, R. D., Toxic effects of the non-  
344 steroidal anti-inflammatory drug diclofenac Part 1: histopathological alterations and  
345 bioaccumulation in rainbow trout. *Aquatic Toxicology* **2004**, *68*, (2), 141-150.
- 346 13. Memmert, U.; Peither, A.; Burri, R.; Weber, K.; Schmidt, T.; Sumpter, J. P.; Hartmann, A.,  
347 Diclofenac: New data on chronic toxicity and bioconcentration in fish. *Environmental*  
348 *Toxicology and Chemistry* **2013**, *32*, (2), 442-452.
- 349 14. Dumont, E.; Williams, R.; Keller, V.; Voss, A.; Tattari, S., Modelling indicators of water  
350 security, water pollution and aquatic biodiversity in Europe. *Hydrological Sciences Journal-*  
351 *Journal Des Sciences Hydrologiques* **2012**, *57*, (7), 1378-1403.
- 352 15. Hannah, R.; D'Aco, V. J.; Anderson, P. D.; Buzby, M. E.; Caldwell, D. J.; Cunningham, V. L.;  
353 Ericson, J. F.; Johnson, A. C.; Parke, N. J.; Samuelian, J. H.; Sumpter, J. P., Exposure  
354 assessment of 17 alpha-ethinylestradiol in surface waters of the United States and Europe.  
355 *Environmental Toxicology and Chemistry* **2009**, *28*, (12), 2725-2732.
- 356 16. Besse, J. P.; Kausch-Barreto, C.; Garric, J., Exposure assessment of pharmaceuticals and their  
357 metabolites in the aquatic environment: Application to the French situation and preliminary  
358 prioritization. *Human and Ecological Risk Assessment* **2008**, *14*, (4), 665-695.
- 359 17. ter Laak, T. L.; van der Aa, M.; Houtman, C. J.; Stoks, P. G.; van Wezel, A. P., Relating  
360 environmental concentrations of pharmaceuticals to consumption: A mass balance approach  
361 for the river Rhine. *Environment International* **2010**, *36*, (5), 403-409.
- 362 18. Oosterhuis, M.; Sacher, F.; ter Laak, T. L., Prediction of concentration levels of metformin  
363 and other high consumption pharmaceuticals in wastewater and regional surface water  
364 based on sales data. *Science of the Total Environment* **2013**, *442*, 380-388.

- 365 19. Carballa, M.; Omil, F.; Lema, J. M., Comparison of predicted and measured concentrations of  
366 selected pharmaceuticals, fragrances and hormones in Spanish sewage. *Chemosphere* **2008**,  
367 72, (8), 1118-1123.
- 368 20. Alder, A. C. B., A.; Carballa, M.; et al; Clara, M.; Joss, A.; Löffler, D.; McArdell, C.S.; Omil, K.;  
369 Tuhkanen, T.; Ternes, T.A., Consumption and occurrence. In *Human pharmaceuticals,*  
370 *hormones and fragrances*, Ternes, T. A. J., A., Ed. IWA Publishing: London, 2006; pp 15-54.
- 371 21. Johnson, A. C.; Williams, R. J., A model to estimate influent and effluent concentrations of  
372 estradiol, estrone, and ethinylestradiol at sewage treatment works. *Environmental Science &*  
373 *Technology* **2004**, 38, (13), 3649-3658.
- 374 22. Joss, A.; Andersen, H.; Ternes, T.; Richle, P. R.; Siegrist, H., Removal of estrogens in municipal  
375 wastewater treatment under aerobic and anaerobic conditions: Consequences for plant  
376 optimization. *Environmental Science & Technology* **2004**, 38, (11), 3047-3055.
- 377 23. Baronti, C.; Curini, R.; D'Ascenzo, G.; Di Corcia, A.; Gentili, A.; Samperi, R., Monitoring natural  
378 and synthetic estrogens at activated sludge sewage treatment plants and in a receiving river  
379 water. *Environmental Science & Technology* **2000**, 34, (24), 5059-5066.
- 380 24. Cicek, N.; Londry, K.; Oleszkiewicz, J. A.; Wong, D.; Lee, Y., Removal of selected natural and  
381 synthetic estrogenic compounds in a Canadian full-scale municipal wastewater treatment  
382 plant. *Water Environment Research* **2007**, 79, (7), 795-800.
- 383 25. Esperanza, M.; Suidan, M. T.; Marfil-Vega, R.; Gonzalez, C.; Sorial, G. A.; McCauley, P.;  
384 Brenner, R., Fate of sex hormones in two pilot-scale municipal wastewater treatment plants:  
385 Conventional treatment. *Chemosphere* **2007**, 66, (8), 1535-1544.
- 386 26. Schaar, H.; Clara, M.; Gans, O.; Kreuzinger, N., Micropollutant removal during biological  
387 wastewater treatment and a subsequent ozonation step. *Environmental Pollution* **2010**, 158,  
388 (5), 1399-1404.
- 389 27. Atkinson, S. K.; Marlatt, V. L.; Kimpe, L. E.; Lean, D. R. S.; Trudeau, V. L.; Blais, J. M., The  
390 occurrence of steroidal estrogens in south-eastern Ontario wastewater treatment plants.  
391 *Science of the Total Environment* **2012**, 430, 119-125.
- 392 28. Jurgens, M. D.; Holthaus, K. I. E.; Johnson, A. C.; Smith, J. J. L.; Hetheridge, M.; Williams, R. J.,  
393 The potential for estradiol and ethinylestradiol degradation in English rivers. *Environmental*  
394 *Toxicology and Chemistry* **2002**, 21, (3), 480-488.
- 395 29. Atkinson, S. K.; Marlatt, V. L.; Kimpe, L. E.; Lean, D. R. S.; Trudeau, V. L.; Blais, J. M.,  
396 Environmental Factors Affecting Ultraviolet Photodegradation Rates and Estrogenicity of  
397 Estrone and Ethinylestradiol in Natural Waters. *Archives of Environmental Contamination*  
398 *and Toxicology* **2011**, 60, (1), 1-7.
- 399 30. Huo, C. X.; Hickey, P., EDC demonstration programme in the UK Anglian Water's approach.  
400 *Environmental Technology* **2007**, 28, (7), 731-741.
- 401 31. Williams, R. J.; Churchley, J. H.; Kanda, R.; Johnson, A. C., Comparing predicted against  
402 measured steroid estrogen concentrations and the associated risk in two United Kingdom  
403 river catchments. *Environmental Toxicology and Chemistry* **2012**, 31, (4), 892-898.
- 404 32. Jobling, S.; Williams, R.; Johnson, A.; Taylor, A.; Gross-Sorokin, M.; Nolan, M.; Tyler, C. R.; van  
405 Aerle, R.; Santos, E.; Brighty, G., Predicted exposures to steroid estrogens in UK rivers  
406 correlate with widespread sexual disruption in wild fish populations. *Environmental Health*  
407 *Perspectives* **2006**, 114, 32-39.
- 408 33. Johnson, A. C.; Williams, R. J.; Matthiessen, P., The potential steroid hormone contribution  
409 of farm animals to freshwaters, the United Kingdom as a case study. *Science of the Total*  
410 *Environment* **2006**, 362, (1-3), 166-178.
- 411 34. Bureau, U. S. C. International database.  
412 <http://www.census.gov/population/international/data/idb/informationGateway.php> (20th  
413 May 2013),
- 414 35. Kostich, M.; Flick, R.; Martinson, J., Comparing predicted estrogen concentrations with  
415 measurements in US waters. *Environmental Pollution* **2013**, 178, 271-277.

- 416 36. Lippert, T. H.; Seeger, H.; Mueck, A. O., Estradiol metabolism during oral and transdermal  
417 estradiol replacement therapy in postmenopausal women. *Hormone and Metabolic*  
418 *Research* **1998**, *30*, (9), 598-600.
- 419 37. Friel, P. N.; Hinchcliffe, C.; Wright, J. V., Hormone replacement with estradiol: Conventional  
420 oral doses result in excessive exposure to estrone. *Alternative Medicine Review* **2005**, *10*, (1),  
421 36-41.
- 422 38. Carballa, M.; Omil, F.; Lema, J. M.; Llompart, M.; Garcia-Jares, C.; Rodriguez, I.; Gomez, M.;  
423 Ternes, T., Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment  
424 plant. *Water Research* **2004**, *38*, (12), 2918-2926.
- 425 39. D'Ascenzo, G.; Di Corcia, A.; Gentili, A.; Mancini, R.; Mastropasqua, R.; Nazzari, M.; Samperi,  
426 R., Fate of natural estrogen conjugates in municipal sewage transport and treatment  
427 facilities. *Science of the Total Environment* **2003**, *302*, (1-3), 199-209.
- 428 40. Zhang, Z. H.; Feng, Y. J.; Gao, P.; Wang, C.; Ren, N. Q., Occurrence and removal efficiencies of  
429 eight EDCs and estrogenicity in a STP. *Journal of Environmental Monitoring* **2011**, *13*, (5),  
430 1366-1373.
- 431 41. Johnson, A. C.; Williams, R. J.; Simpson, P.; Kanda, R., What difference might sewage  
432 treatment performance make to endocrine disruption in rivers? *Environmental Pollution*  
433 **2007**, *147*, (1), 194-202.
- 434 42. Labadie, P.; Budzinski, H., Determination of steroidal hormone profiles along the Jalle  
435 d'Eysines River (near Bordeaux, France). *Environmental Science & Technology* **2005**, *39*, (14),  
436 5113-5120.
- 437 43. Ciparis, S.; Iwanowicz, L. R.; Voshell, J. R., Effects of watershed densities of animal feeding  
438 operations on nutrient concentrations and estrogenic activity in agricultural streams. *Science*  
439 *of the Total Environment* **2012**, *414*, 268-276.
- 440 44. Balaam, J. L.; Grover, D.; Johnson, A. C.; Jurgens, M.; Readman, J.; Smith, A. J.; White, S.;  
441 Williams, R.; Zhou, J. L., The use of modelling to predict levels of estrogens in a river  
442 catchment: How does modelled data compare with chemical analysis and in vitro yeast assay  
443 results? *Science of the Total Environment* **2010**, *408*, (20), 4826-4832.
- 444 45. Johnson, A. C.; Keller, V.; Williams, R. J.; Young, A., A practical demonstration in modelling  
445 diclofenac and propranolol river water concentrations using a GIS hydrology model in a rural  
446 UK catchment. *Environmental Pollution* **2007**, *146*, (1), 155-165.
- 447 46. Ternes, T. A., Occurrence of drugs in German sewage treatment plants and rivers. *Water*  
448 *Research* **1998**, *32*, 3245-3260.
- 449 47. Buser, H. R.; Poiger, T.; Müller, M. D., Occurrence and fate of the pharmaceutical drug  
450 diclofenac in surface waters: Rapid photodegradation in a lake. *Environmental Science &*  
451 *Technology* **1998**, *32*, (22), 3449-3456.
- 452 48. Stumpf, M.; Ternes, T. A.; Wilken, R. D.; Rodrigues, S. V.; Baumann, W., Polar drug residues  
453 in sewage and natural waters in the state of Rio de Janeiro, Brazil. *Science of the Total*  
454 *Environment* **1999**, *225*, (1-2), 135-141.
- 455 49. Heberer, T., Occurrence, fate, and removal of pharmaceutical residues in the aquatic  
456 environment: a review of recent research data. *Toxicology Letters* **2002**, *131*, (1-2), 5-17.
- 457 50. Deng, A. P.; Himmelsbach, M.; Zhu, Q. Z.; Frey, S.; Sengl, M.; Buchberger, W.; Niessner, R.;  
458 Knopp, D., Residue analysis of the pharmaceutical diclofenac in different water types using  
459 ELISA and GC-MS. *Environmental Science & Technology* **2003**, *37*, (15), 3422-3429.
- 460 51. Zwiener, C.; Frimmel, F. H., Short-term tests with a pilot sewage plant and biofilm reactors  
461 for the biological degradation of the pharmaceutical compounds clofibrac acid, ibuprofen,  
462 and diclofenac. *Science of the Total Environment* **2003**, *309*, (1-3), 201-211.
- 463 52. Paxeus, N., Removal of selected non-steroidal anti-inflammatory drugs (NSAIDs), gemfibrozil,  
464 carbamazepine, beta-blockers, trimethoprim and triclosan in conventional wastewater  
465 treatment plants in five EU countries and their discharge to the aquatic environment. *Water*  
466 *Science and Technology* **2004**, *50*, (5), 253-260.

- 467 53. Strenn, B.; Clara, M.; Gans, O.; Kreuzinger, N., Carbamazepine, diclofenac, ibuprofen and  
468 bezafibrate - investigations on the behaviour of selected pharmaceuticals during wastewater  
469 treatment. *Water Science and Technology* **2004**, *50*, (5), 269-276.
- 470 54. Roberts, P. H.; Thomas, K. V., The occurrence of selected pharmaceuticals in wastewater  
471 effluent and surface waters of the lower Tyne catchment. *Science of the Total Environment*  
472 **2006**, *356*, (1-3), 143-153.
- 473 55. Heberer, T.; Feldmann, D., Contribution of effluents from hospitals and private households  
474 to the total loads of diclofenac and carbamazepine in municipal sewage effluents - modeling  
475 versus measurements. *Journal of Hazardous Materials* **2005**, *122*, (3), 211-218.
- 476 56. Wahlberg, C.; Bjorlenius, B.; Paxeus, N., Fluxes of 13 selected pharmaceuticals in the water  
477 cycle of Stockholm, Sweden. *Water Science and Technology* **2011**, *63*, (8), 1772-1780.
- 478 57. Radke, M.; Ulrich, H.; Wurm, C.; Kunkel, U., Dynamics and Attenuation of Acidic  
479 Pharmaceuticals along a River Stretch. *Environmental Science & Technology* **2010**, *44*, (8),  
480 2968-2974.
- 481 58. Andreozzi, R.; Marotta, R.; Paxeus, N., Pharmaceuticals in STP effluents and their solar  
482 photodegradation in aquatic environment. *Chemosphere* **2003**, *50*, (10), 1319-1330.
- 483 59. Tixier, C.; Singer, H. P.; Oellers, S.; Müller, S. R., Occurrence and fate of carbamazepine,  
484 clofibric acid, diclofenac, ibuprofen, ketoprofen, and naproxen in surface waters.  
485 *Environmental Science & Technology* **2003**, *37*, (6), 1061-1068.
- 486 60. Kunkel, U.; Radke, M., Reactive Tracer Test To Evaluate the Fate of Pharmaceuticals in  
487 Rivers. *Environmental Science & Technology* **2011**, *45*, (15), 6296-6302.
- 488 61. Tauxe-Wuersch, A.; De Alencastro, L. F.; Grandjean, D.; Tarradellas, J., Occurrence of several  
489 acidic drugs in sewage treatment plants in Switzerland and risk assessment. *Water Research*  
490 **2005**, *39*, (9), 1761-1772.
- 491 62. Zorita, S.; Martensson, L.; Mathiasson, L., Occurrence and removal of pharmaceuticals in a  
492 municipal sewage treatment system in the south of Sweden. *Science of the Total*  
493 *Environment* **2009**, *407*, (8), 2760-2770.
- 494 63. EEA Waterbase: Urban Waste Water Treatment Directive [http://www.eea.europa.eu/data-](http://www.eea.europa.eu/data-and-maps/data/waterbase-uwatd-urban-waste-water-treatment-directive-3)  
495 [and-maps/data/waterbase-uwatd-urban-waste-water-treatment-directive-3](http://www.eea.europa.eu/data-and-maps/data/waterbase-uwatd-urban-waste-water-treatment-directive-3) (May),
- 496 64. Caldwell, D. J.; Mastrocco, F.; Hutchinson, T. H.; Lange, R.; Heijerick, D.; Janssen, C.;  
497 Anderson, P. D.; Sumpter, J. P., Derivation of an aquatic predicted no-effect concentration  
498 for the synthetic hormone, 17 alpha-ethinyl estradiol. *Environmental Science & Technology*  
499 **2008**, *42*, (19), 7046-7054.

500

501

502